How can a new use of a new and patentable composition be obvious when the composition per se is patentable? The Examiner is again invited to address this issue.

More specifically, claim 27 relates to a method for effecting transdermal migration of a macromolecule comprising applying a pharmaceutical composition to an area of skin of a mammal. This claim uses the identical patented topical pharmaceutical composition as recited in claim 1 of U.S. Patent 5,888,984. Clearly, since the topical pharmaceutical composition recited in claim 1 of U.S. Patent 5,888,984 is novel and non-obvious over the prior art relied upon by the Examiner, the claimed new use of the same composition must be patentable for the same reasons. The Examiner has not addressed this issue.

Claim 28 recites a method for promoting granulation of wounds comprising applying directly to said wound a pharmaceutical composition. This claim uses the identical topical patented pharmaceutical composition as recited in claim 1 of U.S. Patent 5,888,984. Clearly, since the topical pharmaceutical composition recited in claim 1 of U.S. Patent 5,888,984 is novel and non-obvious over the prior art relied upon by the Examiner, the claimed new use of the same composition must be patentable for the same reasons. The Examiner has not addressed this issue.

Claim 29 relates to a method for effecting transdermal migration of a macromolecule comprising applying a pharmaceutical

composition to an area of skin of a mammal. This claim uses the identical patented topical pharmaceutical composition as recited in claim 19 of U.S. Patent 5,888,984. Clearly, since the pharmaceutical composition recited in claim 19 of U.S. Patent 5,888,984 is novel and non-obvious over the prior art relied upon by the Examiner, the claimed new use of the same composition must be patentable for the same reasons. The Examiner has not addressed this issue.

Claim 30 recites a method for promoting granulation of wounds comprising applying directly to said wound a pharmaceutical composition. This claim uses the identical patented pharmaceutical composition as recited in claim 19 of U.S. Patent 5,888,984. Clearly, since the topical pharmaceutical composition recited in claim 19 of U.S. Patent 5,888,984 is novel and non-obvious over the prior art relied upon by the Examiner, the claimed new use of the same composition must be patentable for the same reasons. The Examiner has not addressed this issue.

These issues were discussed during the interview of July 16, 2002. These points were acknowledged by the Examiner's supervisor during the interview of July 16, 2002. However, the Examiner nowhere acknowledges these points in the office action. On the contrary, the Examiner totally ignored Applicants' arguments. Accordingly, an indication of allowance of claims 27-30 or withdrawal of the finality of the Office Action is respectfully

requested.

The Examiner is respectfully requested to specifically refer to the column and line number of the Lowry patent which teaches any composition useful in either of the following methods:

1. A method of transdermal migration of a macromolecule (e.g. claims 1, 2, 4, 5, 7, 8, 11-27 and 29); and

2. A method of promoting granulation of wounds (e.g. claims 3, 6, 9, 10, 28 and 30).

In each of the Office Actions of record, the Examiner has failed to specifically point to any teaching relating to the recited methods. As such, the Examiner has three times failed to comply with Rule 104, part (c)(2). Even if the composition per se was known in the art, which is a point not conceded by Applicants, the Examiner fails to recite any particular part of the reference which teaches that the claimed methods of use are known. Rather, the Examiner asserts that the claimed use is inherent.

The Examiner is respectfully requested to contact the undersigned prior to issuance of any Notice of Allowance. At that point, Applicants will consider adding similar dependent claims on claims 27-30 as in the issued grand-parent application. Such claims have not been added at this time in order to reduce costs for a small entity.

Law of Inherency

The Examiner argues that "the use of essentials oils to increase the permeability of a cell-penetrating component or drug into the skin is inherent within the teachings of Lowry and Williams." Applicants vigorously traverse any allegation of the inherent teachings allegedly attributed to the cited references.

The Federal Circuit stated in In re Robertson, that "to establish inherency, extrinsic evidence must make clear that the missing descriptive matter was necessarily present in the thing described in the reference, and would be so recognized by persons with ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a set of circumstances is not sufficient." In re Robertson, 49 USPQ2d 1949 (Fed. Cir. 1999). Further, it has been held that the mere fact that a certain thing may result from a given set of circumstances is not sufficient, and occasional results are not inherent. MEHL/Biophile International v. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999).

That which is inherent in the prior art, if not known at the time of the invention, cannot form a proper basis for rejecting the claimed invention as obvious under § 103. See *In re Shetty*, 566 F.2d 81, 86, 195 U.S.P.Q. 753, 756-57 (C.C.P.A. 1977).

Shetty claimed a composition of certain adamantine compounds and a method of using them to curb appetite in animals. The

prior art taught structurally similar compounds for use as antiviral agents, with recommended dosages that corresponded to those claimed by appellant. Agreeing with the PTO that the prior art established a *prima facie* case of obviousness as to the composition, which Shetty did not rebut with any evidence of nonobviousness, the CCPA affirmed the rejection of the composition.

But the court did not affirm the PTO position of unpatentability regarding the method claims. Relying on prior art that taught antiviral activity rather than appetite curbing activity, the PTO argued that administering the prior art compound in a dosage described in the art for antiviral effectiveness, which corresponded to appellant's appetite curbing amount, would inherently achieve appetite curbing and thus render the claimed method obvious. Refusing to accept this position, the court responded that although Shetty's dosage "effective to curb appetite' corresponds to or inheres in [the prior art's] amount to 'combat microbial infestation' [, it] does not persuade us of the obviousness of appellant's method." Id. At 86, 195 U.S.P.Q. at 756. Before Shetty had discovered an appetite curbing effect for the claimed adamatane compounds, nothing in the art suggested using the structurally similar prior art adamantanes to curb appetite, much less the claimed dosage amount. Quoting from *In re Spormann*, 363 F.2d 444,448, 150

U.S.P.Q. 449,452 (C.C.P.A. 1966), the court stated:

> [T]he inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.

In re Shetty, 566 F.2d at 86, 195 U.S.P.Q. at 757. See also *In re Naylor*, 369 F.2d 765,768, 152 U.S.P.Q. 106,108 (C.C.P.A. 1966) ("[Inherency] is quite immaterial if. . . one of ordinary skill in the art would not appreciate or recognize the inherent result."); *In re Rijckaert*, 9 F.3d 1531,1533, 28 U.S.P.Q.2d 1955, 1957 (Fed. Cir. 1993)(non chemical case).

In *In re Spormann*, the invention related to a process of producing alkali metal sulfites from alkali metal hydroxides and/or carbonates by spraying the latter, in aqueous solution, into a dry gas containing sulfur dioxide. The temperature and humidity of the gas were set to vaporize the water immediately without producing much sulfate. The chemical reaction in the invention was old, but the conducting of the chemical reaction by spraying an alkali metal compound into the gas stream to cause all the water present to be vaporized immediately was not specifically shown in the prior art. The claimed invention was rejected as being obvious in view of the reference Frederich et al. and other secondary references. Frederich et al. taught a process for making sodium sulfites where a raw material such as sodium hydroxide or sodium carbonate was passed in a solid,

powdered form. The solid material carried a specific amount of water throughout the entire process.

On appeal, the CCPA held that none of the cited references suggested the reduction of sulfate when the reactant gas contained large amounts of oxygen. In addition the CCPA stated that

> the board apparently thought that the minimizing of sulfate production would be *inherent* in the process of Frederich et al…. As we pointed out in *In re Adams…*, the inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is no necessarily known. Obviousness cannot be predicated on what is unknown.

Based on this reasoning, the CCPA reversed the obviousness rejection.

Spormann teaches that arguments based on inherent properties cannot stand when there is no supporting teaching in the prior art. Inherency and obviousness are distinct concepts. Thus, an applicant may in certain circumstances attack an obviousness rejection as improper if the Examiner indicates that specific features of the application, although not shown in the prior art, are inherent.

In conclusion, the Examiner has no basis for alleging that the claimed use is inherent in the prior art.

Rejection of Claims 1-30 Under 35 U.S.C. 103(a)

The only issue remaining in the present application is the rejection of claims 1-30 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 4.900.550 to Lowry in view of Williams. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The Rejection

The Examiner argues, among other things, that:

1) Using essential oils to increase permeability of a cell penetrating drug into the skin is inherent in Lowry and Williams.
2) Lowry teaches several different macromolecules and complex carbohydrates in combination with essential oils, which is readable upon the scope of applicant's claims.
3) Col. 1, lines 54-62 of Lowry teaches that the cosmetic formulation contains a cell penetrating component and essential oil for accelerating cell renewal.
4) Col. 3, lines 50-69 and col. 4, lines 1-15 teaches a cell penetrating component containing hyaluronic acid (0.09-0.11 wt%) and sweet almond oil (0.09-0.11 wt %).
5) Lowry differ from applicants invention "in the scope of complex carbohydrates/essential oils used, the Lowry composition contains hyaluronic acid below 0.3wt% and

essential oil below 2% vol/vol. However, as Williams et al disclose, it was well known….that essential oils were useful as skin penetration enhancers and a wide variety of compounds could be used wit essential oils for transdermal penetration (summary and Table 1).

6) There is a reasonable expectation of success in combining both references to accomplish a therapeutic composition comprising combining the essential oils useful as skin penetration enhancers and a wide variety of compounds for transdermal penetration.

The Lowry Reference

Lowry discloses topical cosmetic compositions and uses thereof as a cosmetic. No pharmaceutical compositions are disclosed.

The Williams Reference

Chemopodium, eucalyptus, ylan ylan and anise were evaluated as penetration enhancers towards 5-fluorouracil. The first paragraph of the Williams reference states that "We have investigated the penetration enhancing activities of some essential oils towards the permeation of 5-fluorouracil (5-FU), chosen as a model polar penetrant, in excised human skin." Table 1 shows increased 5-FU permeation across the skin.

The Present Invention

A first embodiment of the present invention as recited in claim 1 relates to a method for effecting transdermal migration of a macromolecule comprising combining a pharmaceutically effective amount of said macromolecule in a pharmaceutically effective composition with an amount of an essential oil effective to promote transdermal migration of said macromolecule to obtain a mixture of said pharmaceutically effective composition and applying said mixture of said pharmaceutically effective composition to an area of skin of a mammal.

A second embodiment of the present invention as recited in claim 3 relates to a method for promoting granulation of wounds comprising applying directly to said wound a pharmaceutically effective composition comprising a pharmacologically active amount of at least one complex carbohydrate and at least one essential oil in an amount effective to provide penetration of the dermis of a mammal of the complex carbohydrate.

A third embodiment of the present invention as recited in claim 11 relates to a method for effecting transdermal migration of a pharmaceutically effective composition comprising applying said pharmaceutically effective composition to the skin of a mammal, said pharmaceutically effective composition comprising at least one complex carbohydrate of low purity or cosmetic grade and an essential oil in an amount effective to provide transdermal

migration of said pharmaceutically effective composition.

A fourth embodiment of the present invention as recited in claim 27 relates to a method for effecting transdermal migration of a macromolecule comprising applying a pharmaceutical composition to an area of skin of a mammal, wherein said pharmaceutical composition is a topical pharmaceutical composition which comprises as an active ingredient a pharmacologically effective amount of at least one low purity or cosmetic grade complex carbohydrate selected from the group consisting of oligosaccharides, sialylated oligosaccharides, polysaccharides and glycosaminoglycans, and at least one essential oil in an amount effective to allow penetration of the dermis of mammals by the complex carbohydrate.

A fifth embodiment of the present invention as recited in claim 28 relates to a method for promoting granulation of wounds comprising applying directly to said wound a pharmaceutical composition, wherein said pharmaceutical composition is a topical pharmaceutical composition which comprises as an active ingredient a pharmacologically effective amount of at least one low purity or cosmetic grade complex carbohydrate selected from the group consisting of oligosaccharides, sialylated oligosaccharides, polysaccharides and glycosaminoglycans, and at least one essential oil in an amount effective to allow penetration of the dermis of mammals by the complex carbohydrate.

A sixth embodiment of the present invention as recited in claim 29 relates to method for effecting transdermal migration of a macromolecule comprising applying a pharmaceutical composition to an area of skin of a mammal, wherein said pharmaceutical composition comprises as an active ingredient a pharmacologically effective amount of at least one low purity or cosmetic grade complex carbohydrate selected from the group consisting of oligosaccharides, sialylated oligosaccharides, polysaccharides and glycosaminoglycans, and at least one essential oil in an amount effective to allow penetration of the dermis of mammals by the complex carbohydrate.

A seventh embodiment of the present invention as recited in claim 30 relates to a method for promoting granulation of wounds comprising applying directly to said wound a pharmaceutical composition which comprises as an active ingredient a pharmacologically effective amount of at least one low purity or cosmetic grade complex carbohydrate selected from the group consisting of oligosaccharides, sialylated oligosaccharides, polysaccharides and glycosaminoglycans, and at least one essential oil in an amount effective to allow penetration of the dermis of mammals by the complex carbohydrate.

Distinctions Between the Present Invention and the Cited Prior Art

Applicants' Claimed Use is Not Inherent in the Prior Art

Applicant's Representative previously challenged the Examiner by requesting that the Examiner specifically refer to the column and line number of the Lowry patent which teaches any composition useful in either of the following methods:

1. A method of transdermal migration of a macromolecule with a pharmaceutically effective composition (e.g. claims 1, 2, 4, 5, 7, 8, 11-27 and 29); and
2. A method of promoting granulation of wounds with a pharmaceutically effective composition (e.g. claims 3, 6, 9, 10, 28 and 30).

Applicants' representative noted that in each of the Office Actions of record, the Examiner failed to specifically point to any teaching relating to the recited methods. As such, the Examiner has three times failed to comply with Rule 104, part (c)(2). Applicants' representative further argued that even if the pharmaceutical composition per se was known in the art, which is a point not conceded by Applicants, the Examiner fails to recite any particular part of the reference which teaches that the claimed methods of use are known.

In Paper number 7, the most the Examiner states on the subject is that "Lowry discloses the use of several different types of macromolecules and complex carbohydrates in combination

with essential oils which is readable upon the scope of the applicants claims." However, Applicants claim new methods of use rather than compounds or compositions per se. The mere existence of a compound or composition does not destroy the novelty of uses which are not even disclosed in the reference. In this case, the cited references are deficient in failing to disclose both the new use(s) as well as the composition being used. The Examiner should be specific by referring to the column and line number of the Lowry reference which supports a position relevant to the claimed invention, which is directed to new uses of otherwise patentable pharmaceutical compositions. Otherwise, the rejection is moot.

Notwithstanding the interview with the Examiner and his supervisor in July 2002, the Examiner again states in Paper 10 that "Lowry discloses...combination...which is readable upon the scope of the applicants claims." However, the Examiner again fails to recognize that Applicants are claiming novel and nonobvious uses for a pharmaceutical composition that is not even disclosed in the prior art. Indeed, the pharmaceutical composition was found to be patentable over the same art (Lowry) in the parent application. Thus, the Examiner again fails to specifically refer to the column and line number of the Lowry reference which supports his position concerning the claimed methods of use.

The Examiner's Response:

In response to Applicants' challenge to refer to any portion of the Lowry reference expressly teaching or suggesting the claimed uses of a pharmaceutical composition including a method of transdermal migration of a macromolecule and a method of promoting granulation of wounds, the Examiner responds that the claimed use is inherent.

Applicants' Response:

The Lowry reference does not suggest the present invention because the claimed use is not disclosed or suggested, inherently or otherwise. The Lowry reference does not disclose the claimed method of uses with any pharmaceutically effective composition. Alternatively, the Lowry composition contains hyaluronic acid below 0.3 wt.% and essential oil below 2% vol/vol. Therefore, the cosmetic Lowry compositions are not inherently pharmaceutically effective. Thus, the Lowry reference does not suggest the present invention.

Moreover, Applicants do not understand the Examiner's basis for attacking the patentability of the composition *per se*, which was found to be patentable in the parent applications.

Lowry Does Not Disclose a Pharmaceutical Composition As Claimed

The Lowry reference does suggest the claimed use of the pharmaceutical composition. The Examiner's challenge to the patentability of the composition, which is not claimed *per* se in the present application, is inconsistent with allowance of that same or similar composition in the parent application. As pointed out in the parent application, the active ingredient of Lowry is not present in a pharmaceutically effective amount.

The Examiner nowhere acknowledges or responds to Applicants' arguments that a cosmetic composition and a pharmaceutical composition are fundamentally different and that this difference would be readily recognized by one of ordinary skill in the art. At best, the Examiner relies on the description at col. 3, lines 37-38 of Lowry. However, this portion of Lowry merely mentions the well known use of the Lowry cosmetic onto dry skin.

Lowry discloses topical cosmetic compositions and uses thereof as a cosmetic. However, none of the claims of the present invention are directed to cosmetic composition or to the uses of cosmetic compositions. Rather, all of the claims of the present invention are directed to methods using pharmaceutical compositions. A pharmaceutical composition is useful, for example, for treating inflammation, pain or itching. Cosmetic preparations are not useful for "treating" anything. The term "pharmaceutical composition" is not synonomous with a "cosmetic

composition". Moreover, Applicant's novel uses (i.e. method claim(s)) are clearly not taught by Lowry. Rather, the Examiner alleges that the Applicants' claimed use is inherent.

The definition of "pharmaceutical" according to the Random House Dictionary of the English language, page 1079, is a "pharmaceutical preparation, drug..." The definition of "cosmetic" according to the Random House Dictionary of the English language, page 329, is "a powder, lotion or other preparation for beautifying the complexion, skin,hair, nails, etc." It is clear that a cosmetic (e.g. non-drug) as described by Lowry is not a pharmaceutical (e.g. drug) as claimed. The terms "cosmetic" and "pharmaceutical" have well-accepted meanings in the art. The Examiner is ignoring the art-recognized definitions in making this rejection. Lowry does not disclose an effective amount of active ingredient for Applicants' use. Most significantly, Lowry does not disclose the non-obvious use of the claimed composition.

The Lowry reference does not suggest the present invention because the active ingredient is not present in a pharmaceutically effective amount. The Lowry reference does not suggest the present invention since it discloses an amount of essential oil which, in combination with the stated amount of hyaluronic acid is not sufficient to allow penetration of the dermis of mammals by the hyaluronic acid. The Lowry reference nowhere recognizes the claimed use of the claimed pharmaceutical

composition, which itself is not remotely suggested by Lowry, as evidenced by allowance of the parent application.

The description in column 4, line 13 of the Lowry reference discloses that hyaluronic acid is present in an amount of 0.09-0.11 wt.%. The description in column 6, line 17 of Lowry et al. discloses that hyaluronic acid is present in an amount of 0.05-0.10 wt.%. **The amount of hyaluronic acid disclosed in the Lowry reference is not a pharmaceutically effective amount when combined in the low amounts of essential oil disclosed in Lowry.** In order to support Applicant's position, the Examiner's attention is again directed to the prior filed Declaration under 37 C.F.R. 1.132 which shows that when hyaluronic acid is used at a concentration below 0.3 wt.% when combined with 2% vol/vol tea tree oil, the composition will not have pain relieving effect. Thus, the lower amounts of hyaluronic acid and essential oil of the Lowry reference would be pharmaceutically ineffective and thus not fall within the scope of the present invention. However, the failure of Lowry to disclose the claimed use by itself renders the Examiner's rejection moot.

The Examiner should note that the Declaration supports an argument that the cosmetic compositions of the Lowry reference are not pharmaceutical compositions.

These arguments and data were sufficient to overcome the same rejection over the composition claims in the parent

application. Clarification as to why new uses of a patentable composition are not patentable is requested.

Further, the Examiner's comments of record appear to be technically inaccurate. For example, claim 4 recites that the essential oil in the composition is present in an amount of 0.5 to 20% vol/vol. The Examiner alleges that this claimed range overlaps with a range of 0.09-0.11 wt%. Clarification of how the claimed invention overlaps with Lowry is respectfully requested.

In summary, the Lowry reference does not anywhere disclose the claimed methods of use with any pharmaceutical composition. Alternatively, the Lowry composition contains hyaluronic acid below 0.3 wt.% and essential oil below 2% vol/vol. Therefore, the cosmetic Lowry compositions are not pharmaceutically effective. Thus, the Lowry reference does not suggest the claimed methods of use of a separately patentable pharmaceutical composition.

There is No Motivation for modifying the Lowry teachings and converting the cosmetic composition thereof into a pharmaceutical composition.

The Lowry reference is directed to a cosmetic composition. There is no motivation for modifying the teachings of the Lowry reference and converting the cosmetic composition thereof into a pharmaceutical composition. Moreover, the claimed methods of use

are nowhere disclosed in the Lowry reference, inherently or otherwise.

Furthermore, modifying the cosmetic composition of the Lowry reference into a pharmaceutical composition would destroy the teachings thereof. Such hindsight is not allowed. See MPEP 2143 at page 2100-124 (August 2001) and In re Gordon, 221 USPQ USPQ 1125 (Fed. Cir. 1984).

Despite the fact that the MPEP and precedential case law caution the Examiner from making rejections which destroy the teaching of the primary reference in order to obtain the present invention, the Examiner utilizes Applicants' specification as a roadmap and relies on a secondary reference in an attempt to suggest the present invention. Such hindsight is not allowed.

The Lowry reference provides no motivation for carrying any active ingredient transdermally or for promoting the granulation of wounds. The Examiner, recognizing this deficiency, either argues that the use is inherent or alternatively relies on a secondary reference.

Transdermal delivery is the subject of the Williams reference. Ignoring the fact that there is no motivation to combine the teachings of these references, the Examiner's position is that since it is known to use essential oils as penetration enhancers towards 5-fluorouracil, then why not use such enhancers for cosmetics? However, 5-fluorouracil is a drug for battling

cancer. No other drugs are specifically suggested. And even if other drugs were suggested by the Williams reference, the Examiner should recall that the Lowry reference has nothing to do with delivering drugs. Therefore, there is no motivation for combining the teachings of these two references in order to obtain the present invention. Alternatively, combining the teachings of these two references in the manner suggested by the Examiner would destroy the teachings of the primary Lowry reference, which teaches cosmetic compositions. This point is nowhere addressed by the Examiner.

Summary

With respect to the Lowry reference, there is no *prima facie* case of obviousness since the ingredients in the Lowry reference are not present in a pharmaceutically effective amount and because the claimed uses are nowhere disclosed in Lowry. Moreover, the Examiner's position that the claimed uses are inherently described in the Lowry reference is without either legal or factual basis. There is no inherent pharmaceutical use of a cosmetic, especially one which has no pharmaceutical activity. Finally, there is no motivation to combine a reference related to a non pharmaceutically active composition with a reference teaching a pharmaceutically active composition.

Accordingly, in view of the remarks hereinabove, combining the references in the manner suggested by the Examiner does not establish a prima facie case of obviousness. Thus, the rejection should be withdrawn.

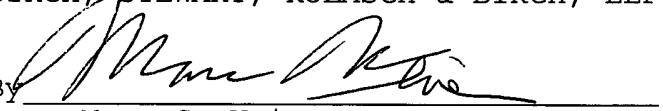
Allowance of all claims is respectfully requested.

If the Examiner has any questions concerning this application, he is requested to contact the undersigned at (703) 205-8000 in the Washington, D.C. area.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By 

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